87. (New) A method according to claim 12, wherein the administration of said agent and said nucleic acid sequence encoding said heterologous protein is performed via a technique chosen among intravenous injection, intravaginal injection, intrarectal injection, intramuscular injection, and intradermic injection.

88. (New) A method according to claim 87, wherein said intravenous injection is selected from the group consisting of retro-orbital sinus injection, tail injection, hepatic injection, femoral injection and jugular injection.

REMARKS

Introduction

Receipt is acknowledged of the office action dated April 24, 2002. In the action, the examiner rejected claims 1-16, 19-22, 27, 29, 30 and 43-47 under 35 U.S.C. § 112 for alleged indefiniteness and non-enablement. The examiner also rejected claims 27 and 43-45 under 35 U.S.C. § 101 for alleged improper definition of a process and objected to claims 5, 11, 14-16, 19-22 and 43-45 as being in improper form. Accordingly, claims 1, 5, 6, 8-14, 16, 19, 21-22, 27, 29, 30, and 43-47 have been amended. Support for these amendments can be found throughout the specification.

New claims 49-88 have been added in the instant application. Accordingly, claims 1-88 are pending in the present application. Support for new claims 49-88 can be found throughout the specification.

In view of the foregoing amendments and the remarks set forth below, reconsideration and withdrawal of the outstanding rejections is respectfully requested.

Claim Objections

The examiner objected to claims 5, 11, 14-16, 19-22 and 43-45 under 37 C.F.R. § 1.75 for allegedly failing to comply with 37 C.F.R. § 1.75(c). Accordingly, claims 5, 11, 14, 16, 19, 21-22 and 43 have been amended to recite "method according to any one of." No new matter has been introduced by these claim amendments.

35 U.S.C. § 101

The examiner rejected claims 27 and 43-45 under 35 U.S.C. § 101 for improper definition of a process. Accordingly, claim 27 has been amended to correctly recite a proper

process claim. Therefore, reconsideration and withdrawal of the rejection is respectfully requested.

35 U.S.C. § 112, 1st Paragraph

The examiner rejected claims 1-16, 19-22, 27, 29-30 and 43-47 under 35 U.S.C. 112 for alleged non-enablement. Specifically, the examiner asserted that "the method of the instant invention would require undue experimentation to gather knowledge on the availability of the heterologous genes, the temporal expression patterns of the endogenous genes as well as their levels of expression and regulation mechanisms and determining the appropriate tolerigenic and/or immunogenic doses such that a skilled artisan would be able to use the appropriate dose to generate a KO of any gene in any mammal" (office action at 9).

Applicant respectfully disagrees. The examiner admitted that "[t]he specification discloses a single example of using the method of the invention in a mouse injected with an adenoviral vector carrying human thrombopoietin (huTPO), wherein said mouse exhibited a functional knockout phenotype for the endogenous mouse TPO" (office action at 8). Accordingly, "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied" (M.P.E.P. § 2164.01, citing *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970)). Applicant directs the examiner to working examples 1.2 and 2.1 beginning on pages 59 and 64, respectively. Additionally, "[f]ailure to disclose other methods by which the claimed invention may be made does not render a claim invalid" " (M.P.E.P. § 2164.01, citing *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533 (1987)).

Additionally, the examiner asserted that the result of locally saturating or inactivating the APCs "varies from on *[sic]* experiment to the other[,] *i.e.*, from one virus stock to another" (office action at 8). Applicant respectfully asserts that this is due to the differences in contamination of the viral stocks, *i.e.*, some stocks comprising a greater concentration of non-competent or wild-type viruses than others. *See,* specification at 35. Evaluating the level of contamination can also be done by routine methods.

Additionally, while the specification teaches that variations in the amount of recombinant virus expressed in pfu/mouse to trigger tolerization can be observed ("these variations being caused by differences in the contamination of viral stocks"), the specifcation

also teaches the preferred amounts of recombinant adenovirus able to form a plaque. *See id.* The specification provides exemplary dosages for depleting or inhibiting at least some antigen presenting cells. For example, as described in a preferred embodiment of the present invention, "the mammal of the invention is an adult mouse and the amount of adenovirus particles administered to deplete or inhibits *[sic]* at least some antigen presenting cells of said mouse is equal to or greater to 10^{10}...particles" (specification at 34, lines 9-13). Preferred dosage ranges are also described. See, *id.*

Although adenovirus was used in the specification as a proof of principle, it is not a limiting example. Adenovirus works via APCs for both the immunogenic induction and the tolerigenic induction. All viruses or pathogens working in the same way, such as those discussed in Drake et al. (2000); Braun et al. (2000); Lapointe et al. (2001); Havenga et al. (2002); Mercier et al. (2002); and Esslinger et al. (2002), should induce the same phenotype.

Additionally, the methods of the present invention may be performed with any secreted membrane protein. Induction of an autoreactive immune response to numerous secreted, membrane or cellular proteins has been previously described in both humans and mice. *See*, Wucherpfunnig *et al.* (1995); Zhao *et al.* (1998); Panoutsakopoulou *et al.* (2001); and Levin (2002). Accordingly, the methods of the present invention are applicable to various heterologous proteins. For your convenience, these references are provided in Appendix A.

Furthermore, the examiner stated that "[t]he state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result" (office action at 7, citing Ross *et al.* (1996)). Applicant respectfully asserts that recent successful gene therapy studies in humans showed that sufficient gene expression induced by direct viral infection (Kay *et al.* (2000)) or enhanced by drugs (Abonour *et al.* (2000)) could produce clinical benefits. Conversely, induction of immune inhibitors may limit the efficacy of such therapies (Ge *et al.* (2001); Gallo-Penn *et al.* (2001)). When the disease is an immunodeficiency, absence of a specific immune response against a virus and a transgene, coupled with a growth selective advantage of the transduced cells, result in the successful gene therapy in human (Hacein-Bey-Abina *et al.* (2002), Aiuti *et al.* (2002)). *See* Appendix B for references.

From the teachings in the specification and working examples, it will be apparent to one skilled in the art that a typical experiment is as follows:

1. Three to four mutants, each one in an adenovirus construction with one of the promoters described on page 49, beginning on line 10, of the instant application. Mutation should maintain a homology of 75%, 85%, 90% and 95%, for example.

2. Three to four dosages of the virus should be $5x10^8$, $1x10^9$, $2x10^9$ and $4x10^9$ (specification at 45).

3. Mouse sera should be tested at 2 months by specific Elisa test to confirm polyclonal activation against the self protein. Elisa test could also be confirmed at four months before phenotypic analysis of the mice. Five to ten mice should be used for each point, which is substantially less than the necessary number of mice used to make a genetic knock-out.

The present application clearly describes that multiple doses of viral particles may be used, from 10^9 pfu to 10^{10} pfu. The inactivation activity (knock-out applications) is close to 10^9 pfu and tolerance (transgenesis applications) is close to 10^{10} pfu. *See*, for example, example 2.1, page 64 of the instant specification.

In light of the foregoing, applicant respectfully requests withdrawal of the enablement rejection.

35 U.S.C. § 112, 2nd Paragraph

The examiner rejected claims 1-16, 19-22, 27, 29, 30 and 43-47 under 35 U.S.C. § 112 for alleged indefiniteness.

The examiner asserted that claims 1-11, 27, 29, 30 and 43-47 are directed to a non-elected invention and that "applicant is required to amend the claims...such that they are drawn only to the elected invention" (office action at 13). Applicant has added claims 49-71 , which comprise the administration of a nucleic acid.

The examiner is reminded that a species election is solely for search purposes and that should the elected species be free of the prior art, the examiner will follow the procedure in M.P.E.P. 803.02 and extend the search to the other species recited in claim 2. Applicant notes that in the instant office action, no prior art was found that anticipates or renders the elected species obvious. Accordingly, the examiner is required to extend the search.

The examiner also asserted that claims 4 and 13 "are indefinite in its recitation of 'a fragment thereof'" and "[i]t is not clear how a fragment of a virus can be selected" (office

action at 13). Applicant respectfully disagrees. As described in the specification, an "agent of the invention is selected on its ability to target the antigen presenting cells, or to be put into contact with APC's" (specification at 28, lines 14-16). When the agent is a virus, one of skill in the art would know, from the selection of viruses exemplified on page 29, lines 1–4 of the instant application, what is meant by "a fragment thereof."

Continuing, the examiner rejected claim 6 as allegedly being "indefinite in its recitation of 'administered prior said heterologous protein'" (office action at 13). As suggested by the examiner, applicant has amended claim 6 to recite "administered prior to said heterolgous protein."

Additionally, the examiner rejected claims 8 and 12 as allegedly "indefinite in their recitation of 'the genome of which comprising'" (*id.*). As suggested by the examiner, applicant has amended claims 8 and 12 to recite "the genome of which comprises."

The examiner also rejected claims 9, 10 and 12 in their recitation of "regulation sequences" (*id.*). As suggested by the examiner, claims 9, 10 and 12 have been amended to recite "regulatory sequences."

Furthermore, the examiner rejected claim 13 in its recitation of "the genome of which not expressing" (office action at 14). As suggested by the examiner, claim 13 has been amended to recite "the genome of which is not expressing."

The examiner rejected claim 20 as being "indefinite in its recitation of 'associated syndromes thereof'" (*id.*). Applicant respectfully disagrees and asserts that one skilled in the art would know what is meant by this phrase. Various diseases are exemplified beginning at the top of page 42 to page 44, line 19.

Furthermore, the examiner rejected claims 21 and 29 for lacking proper antecedent basis for "the therapy" (*id.*). Claims 21 and 29 have been amended accordingly. The spelling error in claim 29 has also been corrected.

According to the examiner, claim 27 is allegedly indefinite where it merely recites a use without any active, positive steps has improper antecedent basis (*id.*). Applicant has amended the claim to obviate the rejection.

The examiner also rejected claims 30, 44, 46 and 47 and 43 and 45 as being indefinite in reciting "chosen among" or "selected among", respectively (office action at 15). Claims 30 and 43-47 have been amended to recite proper markush language.

Claim 47 has also been corrected for spelling errors.

Accordingly, applicant respectfully requests that the indefiniteness rejections be withdrawn.

CONCLUSION

Applicants submit that this application is in condition for allowance, and they solicit an early indication to that effect. Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, a telephone call to the undersigned, at the telephone number listed below, is courteously invited.

Respectfully submitted,

Date 26 August 2002

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VERSION WITH MARKINGS SHOWING CHANGES MADE

1. (Amended) A method [Method] of inhibiting in a mammal formation of neutralizing antibodies directed against a [an] heterologous protein comprising [the step of] co-administering to said mammal, an agent in an amount sufficient to deplete or inhibit at least some antigen presenting cells of said mammal, and a [said] heterologous protein and/or a nucleic acid sequence encoding said heterologous protein, said agent being administered prior to or simultaneously with [to] said heterologous protein and/or [a] nucleic acid sequence, thereby inhibiting the production of neutralizing antibodies against said heterologous protein.

5. (Amended) A method [Method] according to any one of claims 1 to 4, wherein said antigen presenting cells are antigen presenting cells located in the liver of said mammal.

6. (Amended) A method [Method] according to claim 2, wherein said agent is administered prior to said heterologous protein and/or said nucleic acid sequence encoding said heterologous protein.

8. (Amended) A method [Method] according to claim 7, wherein said agent and said nucleic acid sequence encoding said heterologous protein are simultaneously co-administered as a recombinant virus, the genome of which comprises [comprising] at least one nucleic acid sequence encoding said heterologous protein.

9. (Amended) A method [Method] according to claim 8, wherein the genome of said recombinant virus comprises at least regulatory [regulation] sequences necessary to direct the expression of said heterologous protein in at least one antigen presenting cell of said mammal.

10. (Amended) A method [Method] according to claim 9, wherein said regulatory [regulation] sequences comprises promoter sequences selected from the group consisting of [among] cytomegalovirus early promoter (CMV IEP), Rous sarcoma virus long terminal repeat promoter (RSV LTR), myeloproliferative sarcoma virus long terminal repeat (MPSV LTR), simian virus 40 early promoter (SV40 IEP), and major late promoter of the adenovirus.

11. (Amended) A method [Method] according to any one of claims 1 to 10, further comprising [the step of] administering to said mammal an additional agent to enhance the depletion and/or the inhibition of at least some antigen presenting cells of said mammal.

12. (Amended) A method [Method] of inhibiting in a mammal formation of neutralizing antibodies directed against a heterologous protein comprising [the step of] administering to said mammal a recombinant adenovirus, the genome of which comprises [comprising] at least a nucleic acid sequence encoding said heterologous protein and regulatory [regulation] sequences, in an amount sufficient to deplete or inhibit at least some antigen presenting cells of said mammal, thereby inhibiting the production of neutralizing antibodies against said heterologous protein.

13. (Amended) A method [Method] according to claim 12, further comprising [the step of] administering to said mammal additional adenovirus or a fragment thereof, the genome of which is not expressing said heterologous protein, thereby enhancing the amount of adenoviruses to deplete or inhibit at least some antigen presenting cells of said mammal.

14. (Amended) A method [Method] according to any one of claims 12 to 13, wherein said mammal is a mouse and wherein the amount of adenovirus particules administered to deplete or inhibit[s] at least some antigen presenting cells of said mouse is equal or greater to 4.10^{10} particles, said particles comprising optionally said additional adenovirus.

16. (Amended) A method [Method] according to any one of claims 14 to 15, wherein the amount of said recombinant adenovirus able to form plaque, is equal or greater to 4.10^{9} pfu/mouse.

19. (Amended) A method [Method] for reducing an anti-heterologous protein immune response in a mammal, including human, subject to the administration of said heterologous protein and/or nucleic acid sequence encoding said heterologous protein, said method comprising [the step of] inhibiting in said mammal the formation of neutralizing antibodies directed against said heterologous protein by the method according to any one of claims 1 to 16.

21. (Amended) A method [Method] for [the] therapy of a mammal, including humans, afflicted with a disease characterized by the altered expression of an endogenous

protein, said method comprising [the step of] administering to said mammal said protein and/or nucleic acid sequence encoding said protein, and simultaneously or previously, the step of inhibiting in said mammal formation of neutralizing antibodies directed against said protein by the method according to any one of claims 1 to 16.

22. (Amended) A method [Method] according to any one of claims 20 and 21, further comprising [the step of] co-administering simultaneously, separately or sequentially, to said mammal at least one immune modulator[s] selected from the group consisting of [among] cyclosporin, cyclophosphamide, FK506, desoxyspergualine, interleukin-4, interleukin-12, interferon-gamma, anti-CD4 monoclonal antibody, anti-CD8 monoclonal antibody, anti-LFA1 monoclonal antibody, and antibody directed against CD40 ligand or CTLA4Ig.

27. (Amended) A [Use of a] method [according to claim 23] of inhibiting in a mammal formation of neutralizing antibodies directed against a [an] heterologous protein, said method comprising [the step of]:

(i) Optionally, co-administering to a first mammal, at least one agent and said heterologous protein and/or a nucleic acid sequence encoding said heterologous protein, said agent being administered simultaneously, sequentially or separately with said heterologous protein and/or nucleic acid sequence, and determining at least one amount of said heterologous protein and said agent, sufficient to trigger an immune response against said heterologous protein by said first mammal; optionally, re-performing step (i) until said amount is determined;

(ii) co-administering to a second mammal said heterologous protein and/or nucleic acid sequence encoding said heterologous protein, in an amount sufficient to trigger an immune response against said heterologous protein, as determined at step (i) and prior to or simultaneously administering said agent, in an amount greater that the one determined at step (i) and sufficient to trigger an immune response against said agent and sufficient to deplete or inhibit at least some antigen presenting cells of said mammal, and determining for said

second mammal at least one amount of said agent that reduces and/or suppresses the anti-heterologous protein immune response in said mammal; re-performing step (ii) until said amount is determined; and wherein when one co-administers [co-administering] to said mammal said heterologous protein and/or nucleic acid sequence encoding said heterologous protein, and prior to or simultaneously with an [said] agent in an amount equal to or greater than the one determined at step (ii),[.] said mammal produces neutralizing antibodies against said agent but produces no or few neutralizing antibodies against said heterologous protein.

29. (Amended) A method [Method] for [the] therapy of a mammal affected by a disease wherein at least one endogenous protein is involved in said disease etiology [ethiology], said method comprising [the step of] inhibiting the biological functions of said endogenous protein by enhancing the production of neutralizing antibodies against said protein by use of the method according to claim 23.

30. (Amended) A method [Method] according to claim 29, wherein said disease is selected from the group consisting of [chosen among] auto-immune diseases, inflammatory diseases, cancers, viral infections, bacterial infections, parasitic [parasites] infections, and fungal [funguses] infections.

43. (Amended) A method [Method] according to any one of claims 1 to 26 and 33, wherein said heterologous protein or a fragment thereof is selected from the group consisting of [among] the proteins that are presented by class I major histocompatibility molecule (CMH I), a class II major histocompatibility molecule (CMH II), and [or] a combination of a class I major histocompatibility molecule and a class II major histocompatibility molecule.

44. (Amended) A method [Method] according to claim 43, wherein said heterologous protein is selected from the group consisting of [chosen among] secreted proteins, membrane proteins, receptors, intracellular proteins, and nuclear proteins.

45. (Amended) A method [Method] according to claim 44, wherein said secreted protein is selected from the group consisting of [among] neuromediators, hormones, interleukines, lymphokines, interferons, chemokines, and growth factors.

46. (Amended) A method [Method] according to any one of claims 1 to 26 and 33, wherein the mammal is selected from the group consisting of [chosen among] mouse, rat, rabbit, hamster, pig, cow, goat, sheep, horse, and primate.

47. (Amended) A method [Method] according to any one of claims 1 to 26 and 33, wherein the administration of said agent and said heterologous protein and/or nucleic acid sequence encoding said heterologous protein is performed via a technique selected from the group consisting of [chosen among] intravenous injection, intravaginal injection, intrarectal injection, intramuscular injection, and intradermic injection.[,]